REMARKS/ARGUMENTS

After entry of this amendment claims 1, 5, 7-12, 14-15, 19-40 are pending and claims 1-5, 7-12, 14-15, 19-23, 26, and 31-40 are under consideration. Claims 24-25 and 27-30 have been withdrawn from consideration and claims 2-4, 6, 13, claims 16-18 have been canceled, and new claims 31-40 have been added. Claim 1 has been amended to incorporate the element from previous claim 6 (*i.e.*, antibody binds to an epitope within residues 1-12 of Aβ). The claim has also been amended to recite "prophylactically or therapeutically treating" instead of "preventing or treating". Support is provided at *e.g.*, p. 36, lines 14-23. The end of the body of the claim has also been amended to conform to the preamble. Finally, the disease being treated is now defined as being Alzheimer's disease. Support is provided at *e.g.*, p. 2, lines 27-28.

Support for the new claims is provided, *e.g.*, as follows: claim 31, p. 3, line 20; claim 32, p. 36, line 21; claim 33, p. 3, lines 23-30 and p. 37, line 21 to p. 38, line 11; claim 34, p. 42, lines 24-31 and p. 45, lines 1-20; claim 35, p. 37, line 28; claim 36, p. 37, lines 24-25 and 28-29; claim 37, p. 37, lines 29-30; claim 38, p. 45, lines 9-20; claim 39, p. 42, lines 24-31; and, claim 40, p. 3, lines 23-30 and p. 37, line 21 to p. 38, line 11. No amendment should be viewed as acquiescence in any ground of rejection.

The specification has been amended to (1) recite the priority claim under 35 U.S.C. § 120; (2) conform with the replacement drawing sheets submitted herewith; (4) correct an obvious error; and, (3) identify two cell lines producing the 10D5 and 3D6 antibodies, respectively, deposited with the ATTC. Thus, the amendments to the specification contain no new matter.

The paragraphs beginning on page 7, line 12 and p. 59, line 25 describe Figure 10; and to conform with the amendment to Figure 10; both paragraphs have been amended to identify the upper and lower panels of Figure 10 as Figure 10A and 10B, respectively. The paragraphs beginning on p. 7, line 32 and p. 8, line 5 describe Figures 19 and 20, respectively; and, to conform with the amendment to Figures 19 and 20 have been amended to delete "The results for peptide sequence VGSNKGAIIG (SEQ ID NO:32) are shown twice." The paragraphs beginning on p. 16, line 16 and p. 62, line 12 have been amended to replace the plain text font of

genus and species names with an italicized font, *e.g.*, "Salmonella" has been replaced with "*Salmonella.*" The paragraph beginning on page 46, line 19 has been amended to correct an obvious error, *i.e.*, "that binds to A to the patient" has been amended to recite, "that binds to Aβ in the patient" and "of Aβdo not" has been amended to recite "of Aβ do not show."

Applicants deposited the cell line producing the antibody 10D5 and the cell line producing the antibody 3D6 with the ATCC on April 8, 2003. Applicant submits a statement under MPEP § 2406.02 under separate cover. The cell lines deposited with the ATCC are the cell lines producing the antibodies 10D5 and 3D6, respectively, which are identified in the instant specification, Application No. 09/580,518, filed May 26, 2000; U.S. Application No. 322,289 filed May 28, 1999; U.S. Application No. 09/201,430, filed November 30, 1998; and, U.S. Application No. 60/080,970, filed April 7, 1998. Applicants have amended the paragraphs beginning on p. 68, line 17, p. 83, line 14, and p. 107, line 26 of the specification to recite the depository, accession number, and deposit date of the cell lines producing the 10D5 and 3D6 antibodies, respectively. These amendments do not add new matter (*see In re Lundak*, 227 USPQ 90 (Fed. Cir. 1985) and MPEP § 2406.01).

Sequence Listing Requirements

The Office Action takes the position that the instant application fails to comply with 37 C.F.R. §§ 1.821-1.825 because Figures 19 and 20 disclose an amino acid sequence without an appropriate SEQ ID NO. (Applicant respectfully points out that this issue was addressed in Paper No. 14, filed February 18, 2003.) As discussed in the Amendments to the Drawings section, above, Figures 19 and 20 have been amended to delete one of the two occurrences of the sequence "VGSNKGAIIG". The specification has been amended to conform with the replacement Figure 19 and Figure 20 drawing sheets.

Drawings

Amendments to Figure 10

Figure 10 was objected to because the upper and lower panels were unlabeled. The replacement Figure 10 drawing sheet, attached hereto, has been amended to identify the top

panel as "10A" and the bottom panel as "10B." The specification has been amended to conform with the replacement Figure 10 drawing sheet.

Amendments to Figure 11

Figure 11 was objected to because it lacked an appropriate legend. Figure 11 has been amended to include a legend which indicates the treatment group. Support for the amendment to Figure 11 is found at, *e.g.*, p. 7, lines 14-15; and, p. 62, line 23 to p. 63, line 11.

Information Disclosure Statement

The references cited by the information disclosure statements filed September 24, 2001 (Paper No. 6) and September 12, 2002 (Paper No. 11) include all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to Applicant.

Double Patenting

Statutory Double Patenting

U.S. Application No. 09/322,289

Claims 1-12, 14-15, 19-23, and 26 are provisionally rejected for same invention double patenting over claims 1-2, 4-8, and 10-24 of copending U.S. Application No. 09/322,289. Applicant notes rejection of claims 2-4 and 6 is mooted in light of their cancellation. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely that the claims in the cited case will differ from those pending in the current case at the time of allowance of the present case. However, if claims from the different case are in conflict at that time, applicants will amend the claims in the cited case to avoid the conflict.

U.S. Application No. 09/580,015

Claims 1-12, 14-15, 19-23, and 26 are provisionally rejected for same invention double patenting over claims 1-23 and 26 of copending U.S. Application No. 09/580,015. Applicant notes rejection of claims 2-4 and 6 is mooted in light of their cancellation. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely that the claims in the cited case will differ from those pending in the current case at the

time of allowance of the present case. However, if claims from the different case are in conflict at that time, applicants will amend the claims in the cited case to avoid the conflict.

Non-Statutory Double Patenting

U.S. Application No. 09/497,552

Dale B. Schenk is not an inventor of U.S. Application 09/497,552. Thus, the rejection is moot.

U.S. Application No. 09/497,553

Claims 1-12, 14-15, 19-23, and 26 stand provisionally rejected for obviousness type double patenting over claims 42 and 43 of U.S. Application No. 09/497,533. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

U.S. Application No. 09/724,495

Claims 1-12, 14-15, 19-23, and 26 stand provisionally rejected for obviousness type double patenting over claims 1-24, 28-32 and 36-37 and 43 of U.S. Application No. 09/724,495. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

Claim Rejections

Rejection of Claims 1-12, 14-15, 19-23 and 26 Under 35 U.S.C. § 112, First Paragraph

The Examiner says the above claims are enabled for treating Alzheimer's disease via administration of an antibody that specifically binds to an epitope within residues 1-12 of Aβ. However, the Examiner alleges the claims are not enabled for preventing Alzheimer's disease, preventing or treating Down's syndrome or administration of an antibody that binds other components of an amyloid deposit. The claims have been amended to recite prophylactically or therapeutically treating Alzheimer's disease to expedite prosecution without conceding that the Examiner's rejection is warranted on this basis.

Due to the length of the rejection, applicants address the Examiner's comments by paragraph using the numbering of the office action.

¶¶15-17. The Examiner summarizes the basis of rejection, the case law on enablement and the subject matter of the claims. No response is needed.

¶18. The Examiner cites Schenk, Games and Chen as teaching mice that exhibit Alzheimer's-type over-production and build up of anti-Aβ amyloid within the brain. However, the Examiner alleges that it is recognized in the art that these mice do not exhibit Down's syndrome or other amyloidogenic diseases. The Examiner also cites Munch as evidencing lack of correlation between beneficial effects in mice and humans. The Examiner also cites Snipe regarding the breadth of amyloidogenic diseases. Without agreeing with the basis of this rejection, Applicant has, as discussed above, amended the claims to recite prophylactically or therapeutically treating Alzheimer's disease.

¶19. The Examiner alleges that the methods are not effective to prevent onset of disease. The Examiner alleges that all PDAPP mice exhibited plaques regardless of treatment regime. This rejection is moot in view of the amendment to the claims to recite prophylaxis or therapeutic treatment of disease. Prophylaxis is defined at *e.g.*, p. 36, lines 14-19 of the specification and does not require absolute prevention of the disease. In fact, the Examiner's allegation that all PDAPP mice exhibited plaques regardless of treatment is incorrect. When PDAPP mice were treated prophylactically before development of plaques (which starts at about six months), seven of nine mice had no detectable amyloid in the brains (*see* Example 1, particularly, p. 49, lines 9-10). Thus, prophylactic treatment can prevent development of plaques.

¶20. The Examiner cites Dodart and Spooner as supporting uncertainty in the use of Aβ as an immunogen in regard to autoimmunity, general deleterious side effects and variability in the production of anti-Aβ antibodies. However, the present claims are directed to administration of antibodies rather than immunization with Aβ. It is not seen how these issues (which Applicant does not concede in any event) relating to active immunization are relevant to passive immunization as claimed. Moreover, the issue of potential side effects is not necessarily detrimental to enablement as discussed above. The Munch reference (discussed in ¶18 of the Office Action) reports that a small number of patients experienced inflammatory side effects in a human clinical trial of Alzheimer's disease patients. However, the existence of side effects in a small number of patients is consistent with a successful treatment. Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Indeed, it appears from ¶15 of the office action that the Examiner agrees that the reference is not detrimental to enablement of methods of treating Alzheimer's disease.

¶21. The Examiner alleges that the specification fails to provide guidance for the broad range of diseases encompassed by the claims. The Examiner alleges that undue experimentation would be required in de novo determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and/or tissues.

As noted previously, the amended claims are directed to prophylactically or therapeutically treating Alzheimer's disease.

For these reasons, withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3, 6-10, 15, and 19 Under 35 U.S.C. § 102 as Allegedly Anticipated by Walker

Claims 1, 3, 6-10, 15, and 19 stand rejected as anticipated over Walker. Walker is cited as teaching *in vivo* labeling of cerebral amyloid in primates using the mouse antibody 10D5. The Examiner acknowledges that the specificity of the 10D5 antibody is not disclosed in Walker. However, the Examiner notes that the present specification indicates that the specificity

of the 10D5 antibody is for Aβ3-6. The Examiner also notes that the present specification indicates that the isotype of 10D5 is IgG1. This rejection is respectfully traversed.

The present claims (before and after the current amendments) require that the claimed antibodies have a *human* IgG1 isotype. Such is present, for example, in human antibodies, humanized antibodies or chimeric antibodies of the IgG1 isotype. Although practice of the claimed invention is not dependent on an understanding of mechanism, it is believed that the use of antibodies with a human IgG1 isotype is advantageous because this isotype has the highest affinity of human isotypes for the human FcRI receptor on phagocytic cells, and phagocytic cells effect the clearing response of amyloid deposits of Aβ (*see* specification at p. 18, lines 15-17 and Table 16 at p. 97).

The 10D5 antibody discussed by Walker is a mouse antibody. The isotype of this antibody is thus *mouse* IgG1. Not only is mouse IgG1, not a human isotype, it is not even the closest mouse equivalent of human IgG1. As discussed in the specification, the closest mouse equivalent of human IgG1 is mouse IgG2a (*see* p. 21, lines 18-19). Thus, Walker does not disclose or suggest an antibody having a human IgG1 isotype as claimed.

Further, it is submitted that Walker does not disclose a method that results in prophylactic or therapeutic treatment as specified in the amended claims. "Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention," *RCA Corp v. Applied Digital Data Sys. Inc.*, 2212 USPQ 385, 388 (Fed. Cir. 1984). Inherent anticipation cannot be found unless the "prior art *necessarily* functions in accordance with limitations of a process or method claim." (*In re King*, 23 USPQ 136, 138 (Fed. Cir. 1986). (Emphasis supplied.)

Walker does not expressly disclose administration of an antibody to Aβ to a patient so as to achieve prophylactic or therapeutic treatment of the patient. Rather, Walker proposes that antibody be administered for purposes of *in vivo* imaging. If an antibody were administered in a regime that achieved imaging, the same regime would not necessarily prevent or treat Alzheimer's disease (or other disease associated with amyloid deposits of Aβ in the brain). *In vivo* imaging simply requires delivery of sufficient labeled antibody to generate a detectable image. It is not necessary that the antibody clear or prevent deposition of Aβ; indeed,

if the antibody were completely successful in this regard, there would be nothing to label, thereby defeating the purpose of obtaining an *in vivo* image.

In view of the fact that that the requirements of a regime for imaging would not necessarily achieve prophylactic or therapeutic treatment of Alzheimer's disease, Walker does not inherently anticipate the present claims on additional grounds.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

J Liebeschuetz

Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
Attachments (as noted)
RLC:rlc
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